PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 02002030	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/20141	International filing date *(day/month/year)* 26 June 2002 (26.06.2002)	Priority date *(day/month/year)* 27 June 2001 (27.06.2001)
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 31/56 and US Cl.: 514/171, 177, 178		
Applicant SOLVAY PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27 January 2003 (27.01.2003)	02 April 2004 (02.04.2004)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Sreeni Padmanabhan, PhD., Telephone No. (571) 272-0626

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/20141

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed.

☒ the description:
pages 1-42 as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the claims:
pages 43-49 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☒ the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

☐ the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____.

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in printed form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

☒ the description, pages NONE

☒ the claims, Nos. NONE

☒ the drawings, sheets/~~fig~~ NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/20141

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-73	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-73	NO
Industrial Applicability (IA)	Claims	1-73	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Please See Continuation Sheet

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

V. 2. Citations and Explanations:

Claims 1-73 lack of an inventive step under PCT Article 33(3) as being obvious over Rubin (US Patent 5,5059,603), Ebert et al. (US Patent 5,152,997), and Place (US Patent 6,117,446) in view of Langtry et al. (Drugs 1999; 57(6): 967-989), Remington's Pharmaceutical Sciences (1990, 18th ed., pages 1305 and 1314), Merck Index (11th ed., 1989, page 821, monograph 5103), Hofman et al. (US Patent 4,563,473), and Atkinson et al. (US Patent 4,442,094).

Rubin teaches methyl testosterone is useful in a method of treating androgen deficiency associated disorders such as impotence (See particularly col. 2, line 59 - col. 3, line 11).

Ebert et al. teaches testosterone therapy is a useful in a method of treating male hypogonadism and the conditions associated male hypogonadism comprising employing a matrix containing testosterone and penetration enhancer onto the skin (See col. 1, line 20-66).

Place teaches a method of hormonal replacement therapy and symptoms thereof such as female sexual dysfunction and vaginal dryness comprising a treatment of a woman with an estrogen such as estradiol and an androgenic steroid such as testosterone (See col. 11, line 6-61). Place also teaches that the dosage of the estradiol may be 0.05 to 0.5 mg (See col. 11, line 36-61). Place also teaches that the dosage of the androgenic agent such as testosterone to be 0.1 to 2.5mg (See col. 11, line 36-61).

The references do not expressly teach the dosage form of the instant invention to be a gel comprising isopropyl myristate, ethanol, and Carbopol. The references do not expressly teach the employment of the composition containing the combination of testosterone and methyltestosterone or the combination of estradiol and methyltestosterone. The references do not expressly the dosage of methyltestosterone to be 0.2 mg to about 50.0mg and that of testosterone or estradiol to be 0.1g to about 100.0g. The references do not teach the employment of sildenafil in the method herein.

Langtry et al. teaches that sildenafil is useful to treat erectile dysfunction (See abstract).

Remington's Pharmaceutical Sciences teaches that ethanol is a commonly used pharmaceutical solvent (See page 1314-1315). Remington's Pharmaceutical Sciences also teaches that carbopol is a commonly used pharmaceutical excipient as thickening agent (See page 1305).

Merck Index teaches that Isopropyl myristate is useful in topical pharmaceutical preparation where good penetration through skin is desired (See page 821, col. 1).

Hofman et al. teaches that ethanol, Carbopol, and Isopropyl myristate are typical agents for formulating gel (See col. 2, line 19-35).

Atkinson et al. teaches that ethanol, Carbopol, and Isopropyl myristate are typical agents for formulating gel (See col. 4, line 64 - col. 5, line 42).

It would have been obvious to one skill in the art when the invention was made to employ a gel formulation comprising sildenafil and the actives, estradiol and methyltestosterone or testosterone and methyltestosterone, in the dosage herein and ethanol, Carbopol, and Isopropyl myristate as the excipients in a method of treating menopausal disorders in a mammal.

One of ordinary skill in the art would have motivated to employ a gel formulation comprising sildenafil and the actives, estradiol and methyltestosterone or testosterone and methyltestosterone, in the dosage herein and ethanol, Carbopol, and Isopropyl myristate as the excipients in a method of treating menopausal disorders in a mammal because estradiol, testosterone, and

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

methyltestosterone are all known in the art to be useful in method of treating both male and female menopausal disorders. Employing two of these agents which are known to be useful to treat menopausal disorders individually into a single method useful for the very same purpose is *prima facie* obvious. Employing sildenafil with testosterone and methyltestosterone, which are known to be useful in treating impotence individually, in a method useful for the very same purpose would be *prima facie* obvious. Furthermore, the optimization of result effect parameters (e.g., dosage range of the active) is obvious as being within the skill of the artisan. Moreover, interchanging the dosage form of the menopausal disorder treating composition into a gel preparation and employing common excipients in the same is within the purview of skilled artisan.

---------- NEW CITATIONS ----------